REMARKS

Applicants request reconsideration of the above-identified application in view of the foregoing proposed amendments and following remarks.

Applicants have cancelled claims 1-11 and 15. Claim 18 was previously cancelled. Applicants have amended claims 16-17 and 19-22 in reply to the Examiner's rejections as detailed below. Applicants have added new claims 23-26. Support for new claims 23 and 24 can be found in originally filed claims 16 and 17 and on page 20 of the specification. Support for new claims 25 and 26 can be found throughout the specification as originally filed at, for example, pg. 6, line 26 to pg. 7, line 36; pg. 20, line 2 to pg. 21, line 12; and Examples 2 and 3. Claims 23-26 neither add new matter nor require the Examiner to consider the subject matter for the first time. Therefore, claims 16-17 and 19-26 are now pending in this application.

Cancellation of claims 1-11 and 15 is done so without prejudice and without waiver of applicants' rights to file for and obtain claims directed to any non-elected subject matter in divisional or continuing applications which claim priority from this application under 35 U.S.C.§ 120. In addition, any amendments are made without waiver of

applicants' rights to continue to prosecute and obtain claims directed to the former subject matter either in this application or in other applications.

None of the proposed amendments or added claims presents new matter.

The Rejections

35 U.S.C. § 112, Second Paragraph: Indefiniteness

Claims 16, 17 and 19-22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The rejection is detailed below in sections A-G.

A. Claims 16, 17, 19-22 (JNK3 Protein): The Examiner asserts that in claims 16, 17 and 19-22 it is not clear which JNK3 protein is meant because "it is known that there is a plurality of JNK3 proteins." The Examiner also asserts that in claims 16, 17 and 20 it is unclear to which JNK3 protein the particular amino acid residues listed refer.

A person skilled in the art would recognize that JNK3 refers to JNK3α. JNK3α has only two isoforms: JNK3α1 and

JNK3α2, which have identical sequences for amino acid residues 45-400. See, Gupta et al., The EMBO Journal, Vol. 15 No 11, pp. 2760-2770, 1996. In addition, United States patent 6,943,000; effective filing date 10/03/1997 ("Davis") lists GenBank accession numbers U34819, U34820, U07620, L27128, L3523 on page 28, columns 3 and 4 in the definition of "JNK3." These GenBank entries refer only to JNK3α1 or JNK3α2. Thus, applicants request the Examiner withdraw this rejection.

B. Claim 16 (Figure 1A): The Examiner has rejected claim 16 as allegedly being indefinite as it addresses "coordinates according to Figure 1A" while "said Figure does not provide any coordinates."

Applicants respectfully note that Amendments to the Specification and Drawings were made in a September 18, 2003 Amendment and Reply to Office Action.* In this Amendment and Reply, the applicants relabeled original "Figure 1" to "Figure 1A" and original "Figure 1A" to "Figure 1B" in the Drawings and Specification. At that time, applicants also submitted a set of replacement drawing sheets to the Official Draftsperson

* A copy of the September 18, 2003 Amendment and Reply to Office Action is provided herewith as Exhibit A.

for Correction of Informalities under 37 C.F.R. § 1.85.** Thus, replacement Figure 1A in fact provides the atomic coordinates of JNK3. Replacement Sheets 1/69 to 61/69 obviate the Examiner's rejection. Thus, applicants request the Examiner withdraw this rejection.

C. Claims 16, 17 and 19 (binding pocket comprises coordinates): The Examiner has rejected claims 16, 17 and 19 as allegedly being indefinite because it is unclear how a binding pocket may comprise coordinates. Further, the Examiner contends that the claim may be "construed as reading on either *in vitro* or *in silico* methods."

Applicants have amended claims 16 and 17 to recite "using" atomic coordinates and binding pockets comprising amino acids. Thus, amended claims 16 and 17 (and dependent claim 19) clarify that the amino acids comprise the binding pocket and that these amino acids are described by the coordinates in Figure 1A. This amendment also clarifies that claims 16 and 17 (and dependent claim 19) read on *in silico* methods because the *structure coordinates* are used. As

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** A copy of the Transmittal Letter of Replacement Drawing Sheets is provided herewith as Exhibit B; Copies of Replacement Sheets 1/69 to 61/69 are provided herewith as Exhibit C.

amended, claim 16 and 17 obviate the Examiner's rejection to claims 16, 17 and 19. Thus, applicants request the Examiner withdraw this rejection.

D. Claims 16 and 20 (using all or part of steps): The Examiner has rejected claims 16 and 20 as allegedly being unclear because these claims fail to "specify with particularity what the method steps are" when referring to "using" all or part of a binding pocket (claim 16) or coordinates (claim 20). The Examiner contends that such a claim is confusing as it does not "specify any positive steps involved in the process of 'using.'" Applicants traverse.

The methods involved in "using" all or part of a binding pocket (claim 16) or "using" all or part of coordinates (claim 20) would be apparent to one of skill in the art. Specifically, page 20, line 2 to page 21, line 6 and page 21, line 28 to page 22, line 28 in the specification teaches methods and techniques for identifying new chemical entities which may interact with the JNK3 binding pocket, wherein factors for the design of such compounds as well their preferred characteristics are presented. In addition, a plurality of specialized computer programs, which may assist one skilled in the art in the process of selecting chemical

entities capable of interacting with the JNK3 binding pocket, are described on page 22, line 34 to page 27, line 5 in the specification. One skilled in the art who is familiar with these programs, methods and techniques would understand how to use the coordinates. Thus, applicants request the Examiner withdraw this rejection.

E. Claims 16 and 20 (using to design): The Examiner has rejected claims 16 and 20 as allegedly being indefinite due to "lack of clarity of the claim language 'using to design inhibitor'" for "failing to recite a final process step which agrees back with the preamble." The Examiner asserts that "there is no indication how the inhibitor is defined" and that the "metes and bounds of the claim" should be clarified "via clearer claim wording." The Examiner suggests incorporating the limitations of claims 19 and 21 into claims 16 and 20, respectively.

Applicants have amended claims 16 and 20 to recite a method for "designing" an inhibitor so as to recite the basic step of designing an inhibitor in a positive, active fashion. Support for this amendment may be found throughout the specification as filed, for example, on page 21, line 13 to page 22, line 28. As amended, claims 16 and 20 obviate the

Examiner's rejection because the final step "to design or select" now agrees back with the preamble "method of designing". Thus, applicants request the Examiner withdraw this rejection to claims 16 and 20.

F. Claim 16 (all or part of a binding pocket): The Examiner has rejected claim 16 as indefinite. Specifically, the Examiner contends that claim 16, part b), is unclear as to what is meant by "part of a binding pocket" and as to what "part" is sufficient for the method. Applicants have amended claim 16, part b), to delete "all or part of." Support for this amendment is found on page 8 lines 15-30. As amended, claim 16 obviates the Examiner's rejection. Thus, applicants request the Examiner withdraw this rejection to claim 16.

G. Claim 20 (all or part of said coordinates): The Examiner has rejected claim 20 as indefinite. Specifically, the Examiner contends that claim 20, part c), is unclear as to what is meant by "part of coordinates" and as to what "part" is sufficient for the method. Applicants have amended claim 20, part c), to delete "all or part of" so as to clarify the method. Support for this amendment is found on page 18, line 24 to page 19, line 19. As amended, claim 20 obviates the

Examiner's rejection. Thus, applicants request the Examiner withdraw this rejection.

In summary, applicants have commented on each of the Examiner's § 112, second paragraph rejections and made amendments in reply to these rejections. Given applicants' above comments and amendments, applicants request that the Examiner reconsider the rejections detailed in sections A-G and withdraw all § 112, second paragraph rejections.

35 U.S.C. § 112, First Paragraph: Enablement

Claims 16, 17 and 19-21 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that "the specification, while being enabling for designing a ligand for JNK3α1 protein, does not reasonably provide enablement for any other JNK3 protein." Specifically, the Examiner asserts that all working examples are directed to JNK3α1 and the "specification does not guide how to use the invention as claimed with other JNK3 proteins having different amino acid content." Applicants traverse.

It is commonly known in the art that JNK3 refers to JNK3α. While the specification teaches that the preferred embodiment is JNK3α1 (see page 8, lines 1 to 3), it is known

in the art that both JNK3α isoforms, JNK3α1 and JNK3α2, have identical amino acid content and sequence for amino acid residues 45-400, the residues present in the protein which was crystallized in the present invention (see Gupta el al., Figure 1, page 2762). The Examiner states in his rejection that "using coordinates of JNK3α1 addressed in the instant specification, one skilled in the art will not be able to design inhibitors to any other protein having different amino acid sequence" (see paragraph 2, page 5 of May 8, 2006 Office Action). Applicants submit that JNK3α1 and JNK3α2 have the same amino acid sequence and therefore one skilled in the art would be able to design inhibitors for both isoforms. Given at least the above reasons, applicants request the Examiner withdraw the § 112, first paragraph rejection.

35 U.S.C. § 103: Obviousness

Su et al. (US 6,162,613): Claims 16, 17 and 19 stand rejected under 35 U.S.C. § 103 as being unpatentable over United States patent 6,162,613 ("Su"). The Examiner asserts that claim 6 of Su discloses a method for identifying an inhibitor of JNK3 which is "based upon identification of residues in the ATP-binding pocket of [a] kinase by crystallizing the kinase." The Examiner further asserts that

although this method disclosed by Su does not specify the atomic coordinates of JNK3 according to Figure 1A, "the specific limitations of atomic coordinates in this instant case do not distinguish the invention from the prior art in terms of patentability because they are descriptive nonfunctional subject matter." Examiner disagrees with applicants' previously presented argument that the structure coordinates are functional descriptive matter. Applicants traverse. Applicants contend that there is a fundamental difference between the method taught by Su and that taught by the present invention.

Su generally teaches a method for identifying an inhibitor of JNK3 by: (1) taking a known serine/threonine or tyrosine kinase ("kinase-1") crystallized with a known inhibitor (or compound) to its ATP-binding site; (2) identifying the amino acids that comprise close contacts between the known inhibitor and ATP-binding site of kinase-1; (3) aligning some but not all of the amino acids of kinase-1 ATP-binding site with amino acids of a different serine/threonine or tyrosine kinase ("kinase-2"); (4) altering the amino acids of the identified kinase-2 ATP-binding site to produce a mutant serine/threonine or tyrosine kinase ("mutant-kinase-2"); (5) determining which mutant-kinase-2 molecule

binds the known inhibitor with greater affinity over that of the kinase-2 molecule; and (6) using this information (via molecular modeling) to alter the known inhibitor to create a *new* inhibitor to the kinase-2 molecule with greater binding affinity than that of known inhibitor. Independent claim 1 of Su generally recites these steps and dependent claim 2 identifies the kinase-1 and kinase-2 of claim 1 as mitogen activating protein (MAP) kinases. Claim 6 of Su depends from claim 2 and further defines kinase-2 as ERK2 or JNK3. In short, claim 6 of Su recites a method of designing inhibitors which involves both using two different protein molecules and mutating the JNK3 (kinase-2) molecule. Su does not teach or suggest crystallizing JNK3.

In contrast, amended claims 16, 17 and 19 of the present invention are directed to methods of identifying or designing inhibitors *directly* using the structure coordinates of the *actual JNK3* binding pocket. The present invention teaches the structure coordinates and the three-dimensional representation of JNK3. In addition, the present invention teaches using these structure coordinates in a method to design or identify inhibitors of JNK3. Unlike Su, the present invention does not teach using two different protein molecules. The present invention also does not teach mutating

JNK3 in the method of identifying or designing inhibitors of JNK3. One skilled in the art would recognize that the method of the present invention is very different from the method recited in Su. Not only does Su fail to disclose a method of identifying an inhibitor using one molecule, but also Su teaches away from the method in the present invention. Thus, Su should not render the present invention obvious.

Furthermore, applicants maintain that the JNK3 atomic coordinates in the instant application *are* descriptive functional subject matter. A functional relationship exists between the computer and data stored therein - the computer converts novel structure coordinates (that were not available prior to this invention) into a display of a novel three-dimensional representation of a binding site of an unphosphorylated JNK3 protein.

For at least the reasons above, the method prevented in Su does not render the present invention obvious. Thus, applicant request that the Examiner withdraw this rejection to claims 16, 17 and 19.

Davis et al. (US 6,943,000) in view of Gupta et al.: Claims 20-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over United States patent 6,943,000; effective

filing date 10/03/1997 ("Davis") in view of Gupta et al., The EMBO Journal, Vol. 15 No 11, pp. 2760-2770, 1996 ("Gupta"). The Examiner contends that Davis is "directed to the identification and use of JNK3 modulators" and "teaches that computer modeling is used to identify compounds that modulate activity of a JNK3 protein by reacting, for example with its active site." The Examiner additionally asserts that the active site of JNK3 can be identified using methods known in the art, such as X-ray crystallography, and that once the structure of the active site has been determined, candidate modulating compounds can be identified so that said compounds have structures which match the active site of the structure. The Examiner also contends that the method of Davis is "applicable to any of known JNK3 proteins" and that the reference "teaches that there is a plurality of JNK3 proteins known."

Although Davis "does not teach use of a JNK3 protein having the particular residues addressed in claim 20, part(b)", the Examiner contends Davis is not directed to any particular JNK3 isoform. Thus, the Examiner asserts it would be *prima facie* obvious to any artisan that any JNK3 protein of interest can be used in the method of Davis. The Examiner also asserts that while Davis does not address the use of a

truncated JNK3 protein, the reference does not teach that identifying an inhibitor requires the full-length protein but rather states that a digital model of the *active site* is required. Applicants traverse. It would not be *prima facie* obvious to one skilled in the art that inhibitors of any JNK3 protein could be identified using the method of Davis in view of Gupta.

The three basic criteria for a prima facie case of obviousness are: (1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) a reasonable expectation of success; and (3) teaching or suggestion of all claim limitations by the prior art reference (or references when combined). See, M.P.E.P. §2143. The required criteria for a finding of prima facie obviousness can not be found in the present case.

First, a reasonable expectation of success does not exist. The present invention teaches for the *first time* the crystal structure of unphosphorylated JNK3 and the set of amino acids that comprise the binding pocket of the unphosphorylated JNK3 molecule. It is readily accepted that

the method of x-ray crystallography is an unpredictable art. Both producing a crystal of a protein and determining the three-dimensional structure of a protein are unpredictable, meticulous and iterative processes. Crystallization and heavy atom screening, two basic but essential elements of using x-ray crystallography to solve a protein structure, involve trial-and-error steps that result in a high degree of failure. Given this unpredictability in this art, a reasonable expectation of success according to Davis in view of Gupta , which is required in order to establish a *prima facie* case of obviousness, does not exist.

Second, Davis and Gupta fail to teach or suggest each and every element of claims 20-22. Specifically, neither Davis, Gupta, nor Davis in combination with Gupta, teach or suggest the steps of producing a crystal of an unphosphorylated JNK3 and of determining the three-dimensional atomic coordinates. Davis is not enabled to produce a crystal of JNK3 nor is Davis enabled to determine the three-dimensional structure of JNK3.

Neither Davis, Gupta nor a combination of Davis and Gupta teach or suggest each element of claim 20. In addition, the art of x-ray crystallography is too unpredictable to yield reasonable expectation of success. Thus, Davis in view of

Gupta is not prima facie obviousness. For at least the above identified reasons, applicants respectfully request reconsideration and withdrawal of the § 103 rejection to claims 20-22.

CONCLUSION

Applicants respectfully request that the Examiner reconsider and withdraw all outstanding objections and rejections, enter the amendments, and pass the resulting claims to allowance.

Respectfully submitted,

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